Potential Use of Omega-3 Fatty Acids in Trauma, Brain Injury, and Psychiatric Issues

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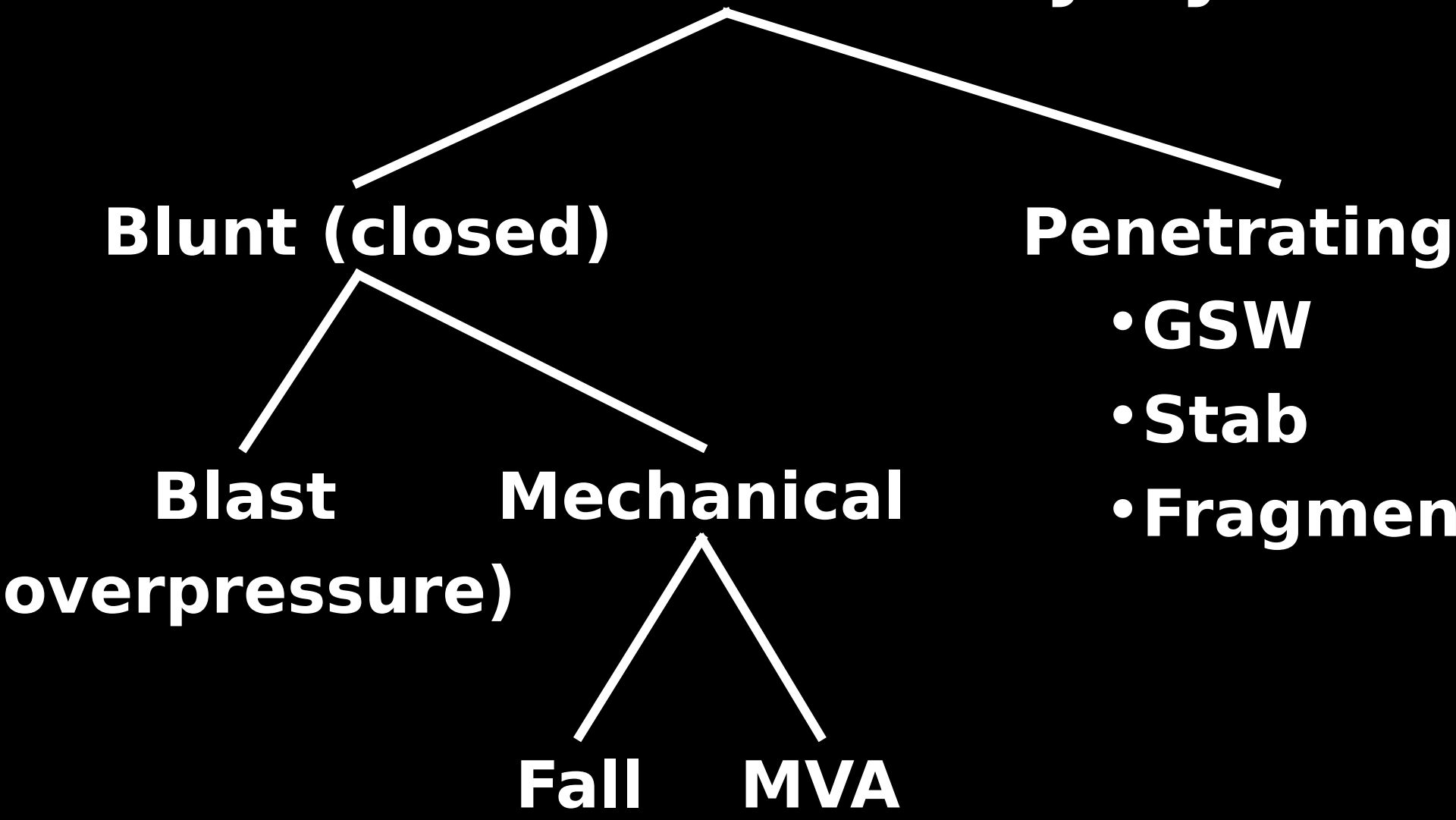
Traumatic Brain Injury



Traumatic Brain Injury Description

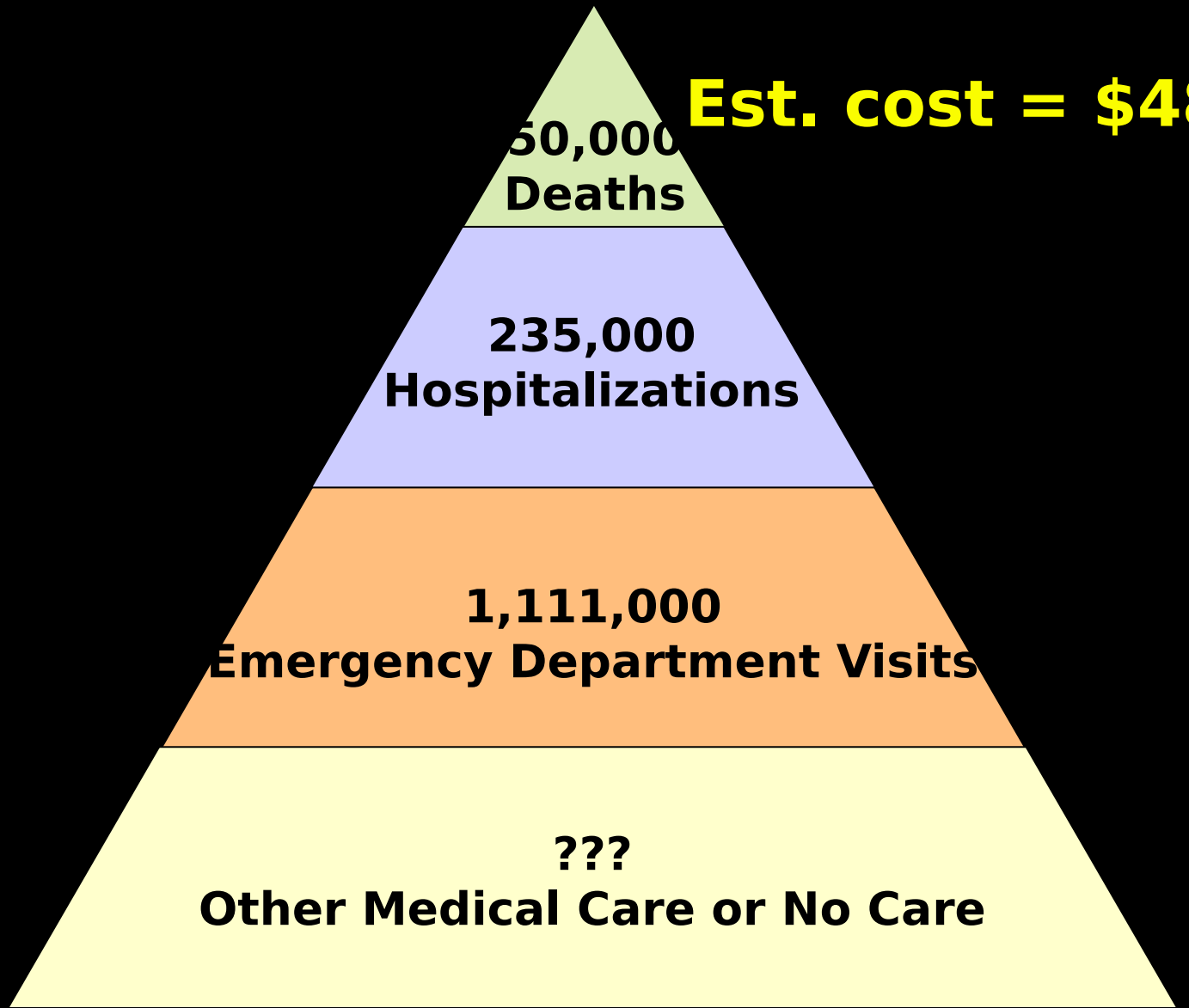
Severity	GCS	LOC	PTA
Mild	13–15	<20 min-1 hr	<24 hr
Moderate	9–12	1 – 24 hrs.	> 24 hrs. - <7days
Severe	3–8	>24 hrs.	>7 days

GCS = Glasgow Coma Scale
LOC = Loss of consciousness
PTA = Posttraumatic amnesia

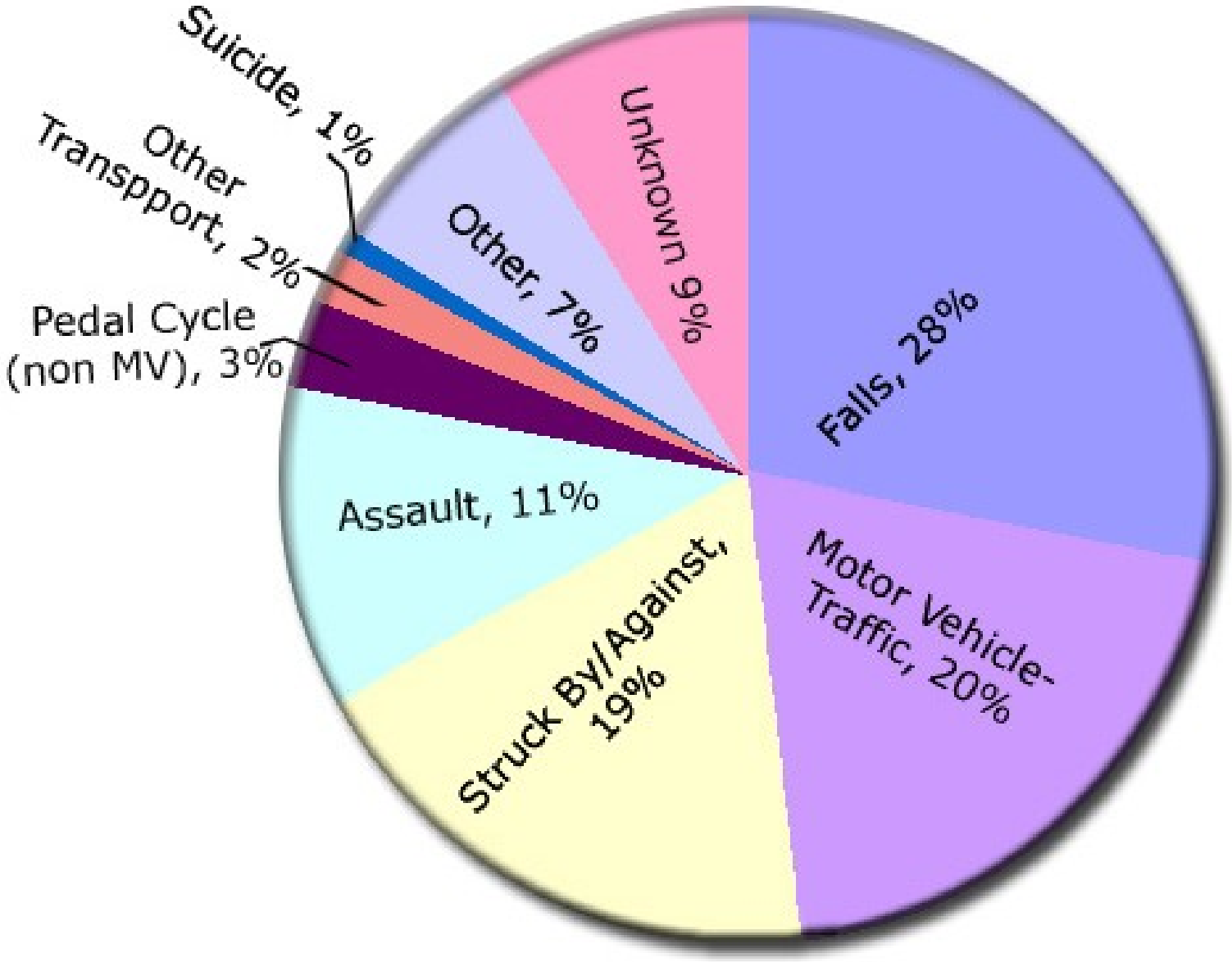
Relative Proportion of Levels of Care for TBI

Uniformed Services University – Department of Preventive Medicine and Biometrics

Source: CDC: Traumatic Brain Injury in the United States, October 2004



Est. cost = $48B/yr


Suicide, 1%
Other Transpport, 2%
Pedal Cycle (non MV), 3%
Other, 7%
Unknown 9%
Falls, 28%
Assault, 11%
Struck By/Against, 19%
Motor Vehicle-Traffic, 20%

OIF/OEF TBI Experience

Between January 2003 and March 31, 2008 DVBIC military, VA and civilian sites have seen a total of 6,602 TBI pts

Of 433 WRAMC patients with TBI (1/03 to 4/05)

- **68% of injuries were due to explosion/blast**
- **88.5% were closed TBI**
- **Post Traumatic Amnesia (PTA) $\leq$ 24 hours: 43%**
- **Complications - 14% shock; 9.5% hypoxia; 25% skull fracture; 18.7% subdural hematoma; and 1.5% epidurals**
- **19% had limb amputations; lower extremity most common**

Warden et al., Journal of Neurotrauma 2005; 22:1178

Neuropathology of Closed TBI

Primary Injury:

- Contusions/Hemorrhages
- Diffuse Axonal Injury (DAI) - degeneration of axons' distal projections and to diffuse loss of synaptic terminals (hours to days)

Secondary Injury (Intracranial):

- Blood Flow and Metabolic Changes
- Traumatic Hematomas
- Cerebral Edema
- Hydrocephalus
- Increased Intracranial Pressure

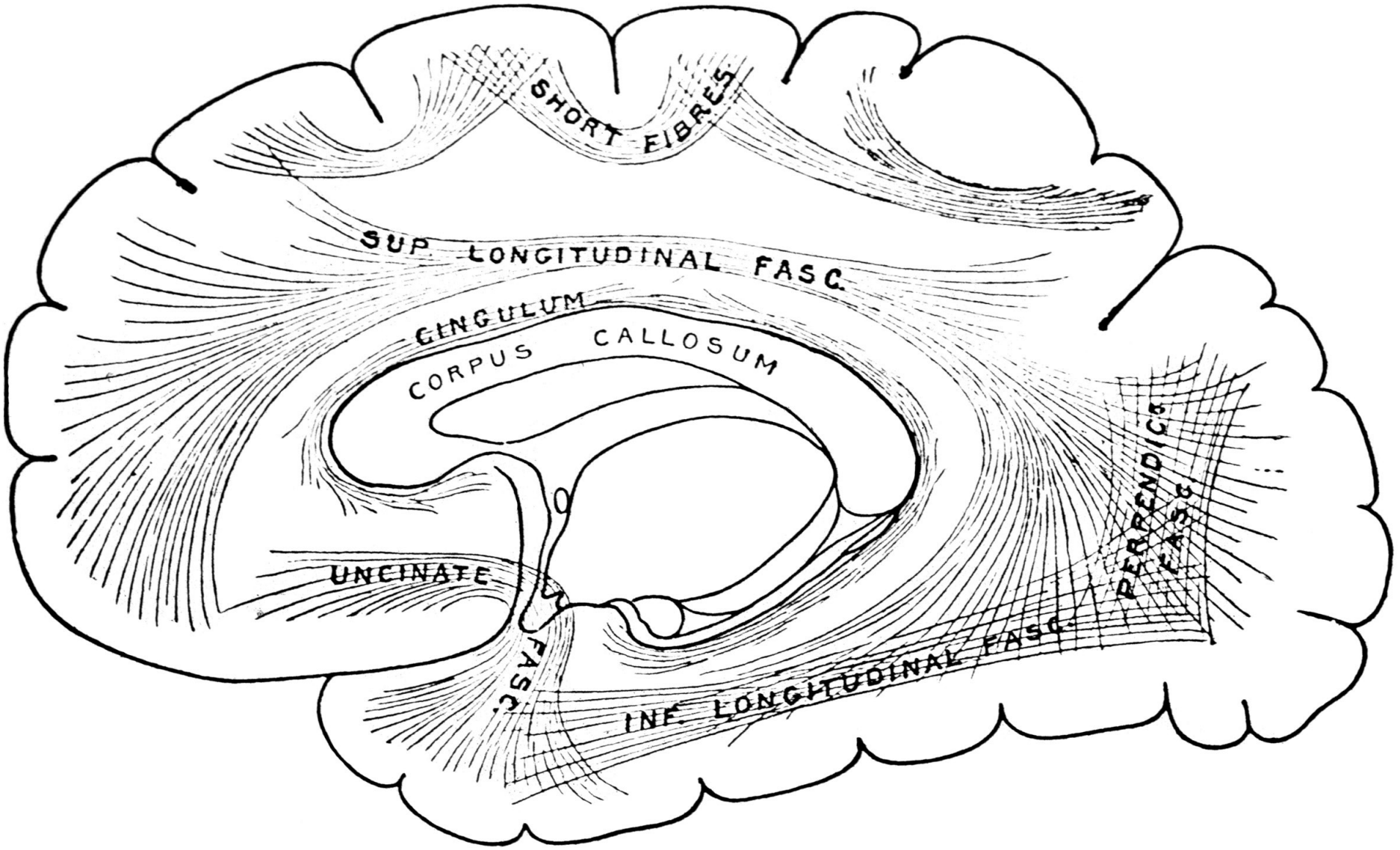
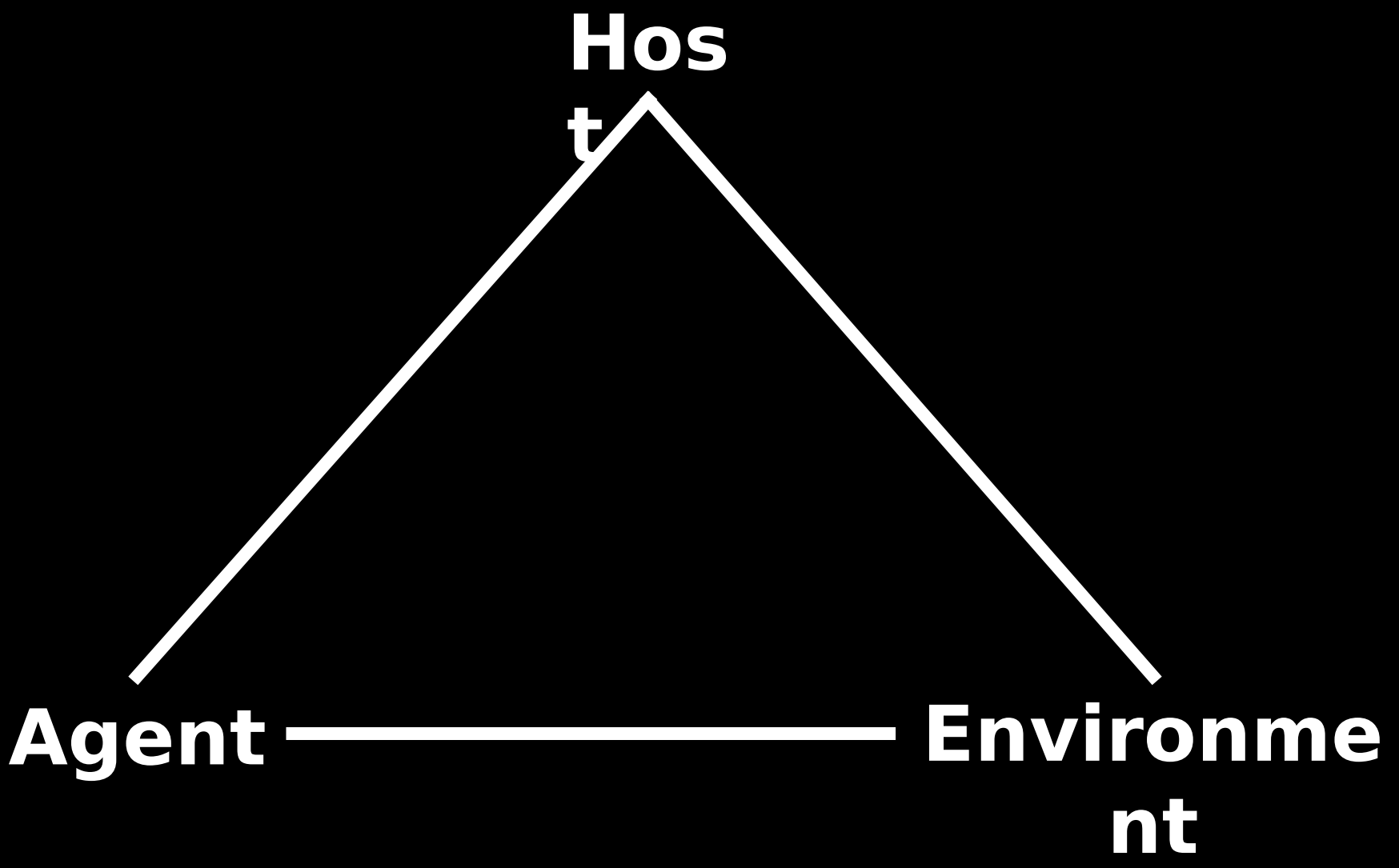


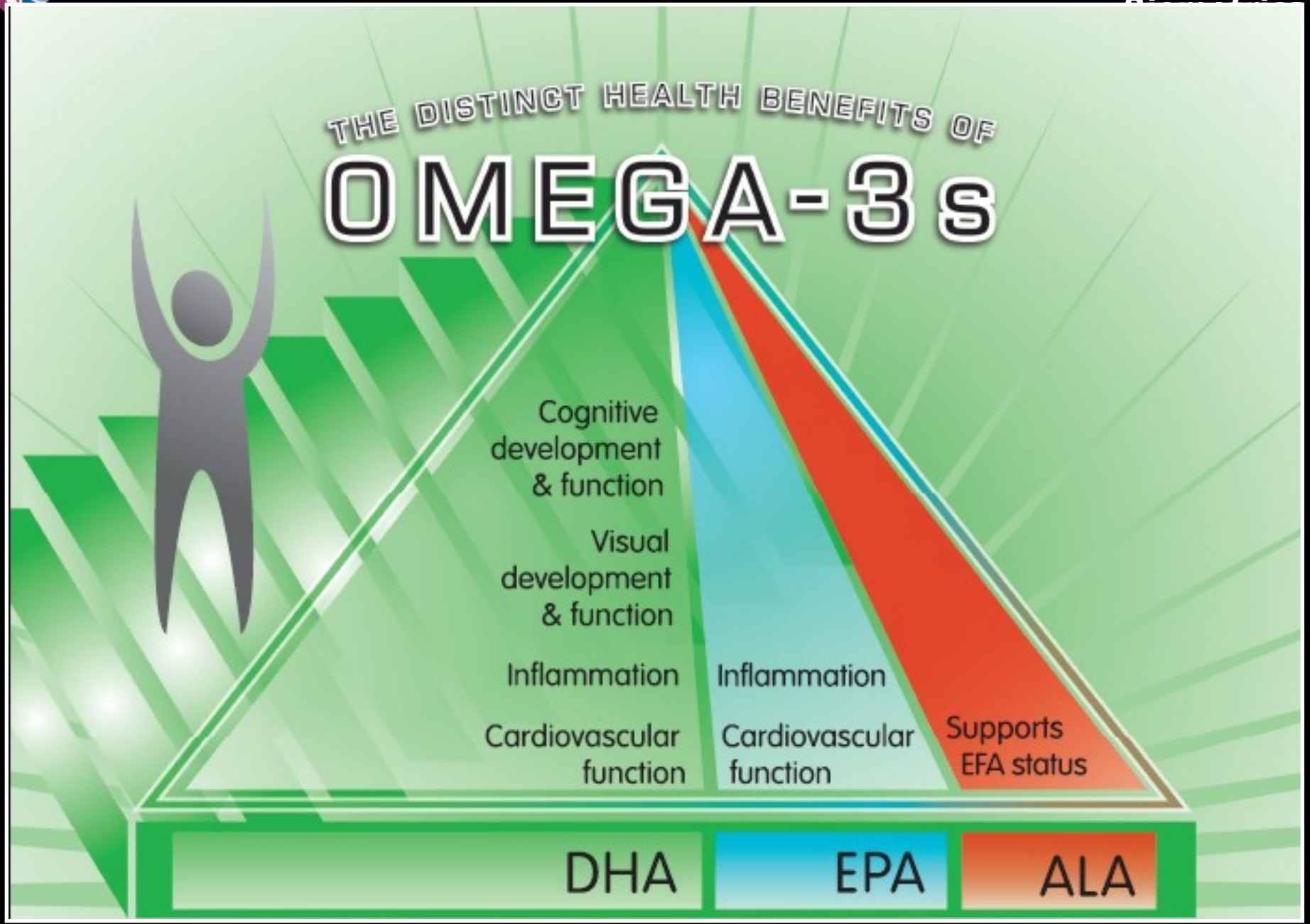
FIG. 11–73.—Diagram showing principal systems of association fibers in the cerebrum.

Treatment Areas

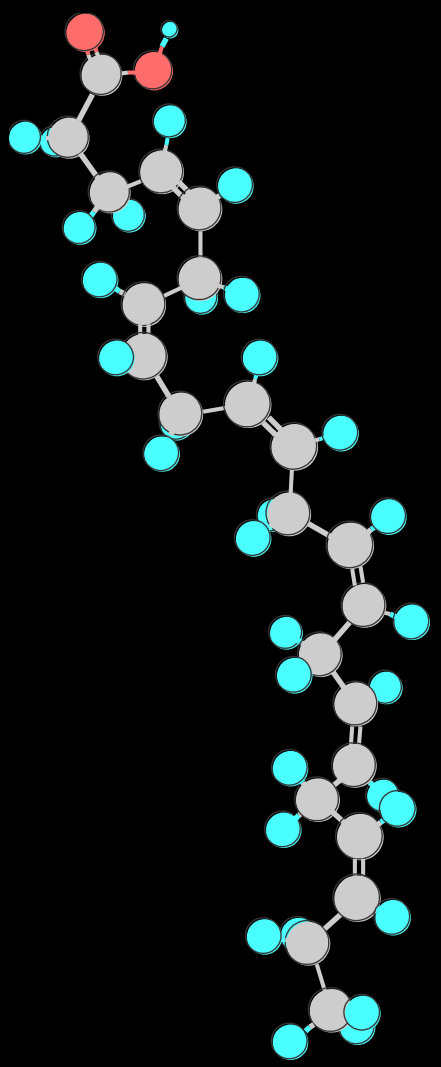
- Education and support for the patient's family
- Rest and avoidance of another injury
- Individual and group therapies
- Medication including symptom mgt
- Rehab (acute, sub-acute, community re-entry)

Epidemiologic Triad of Disease



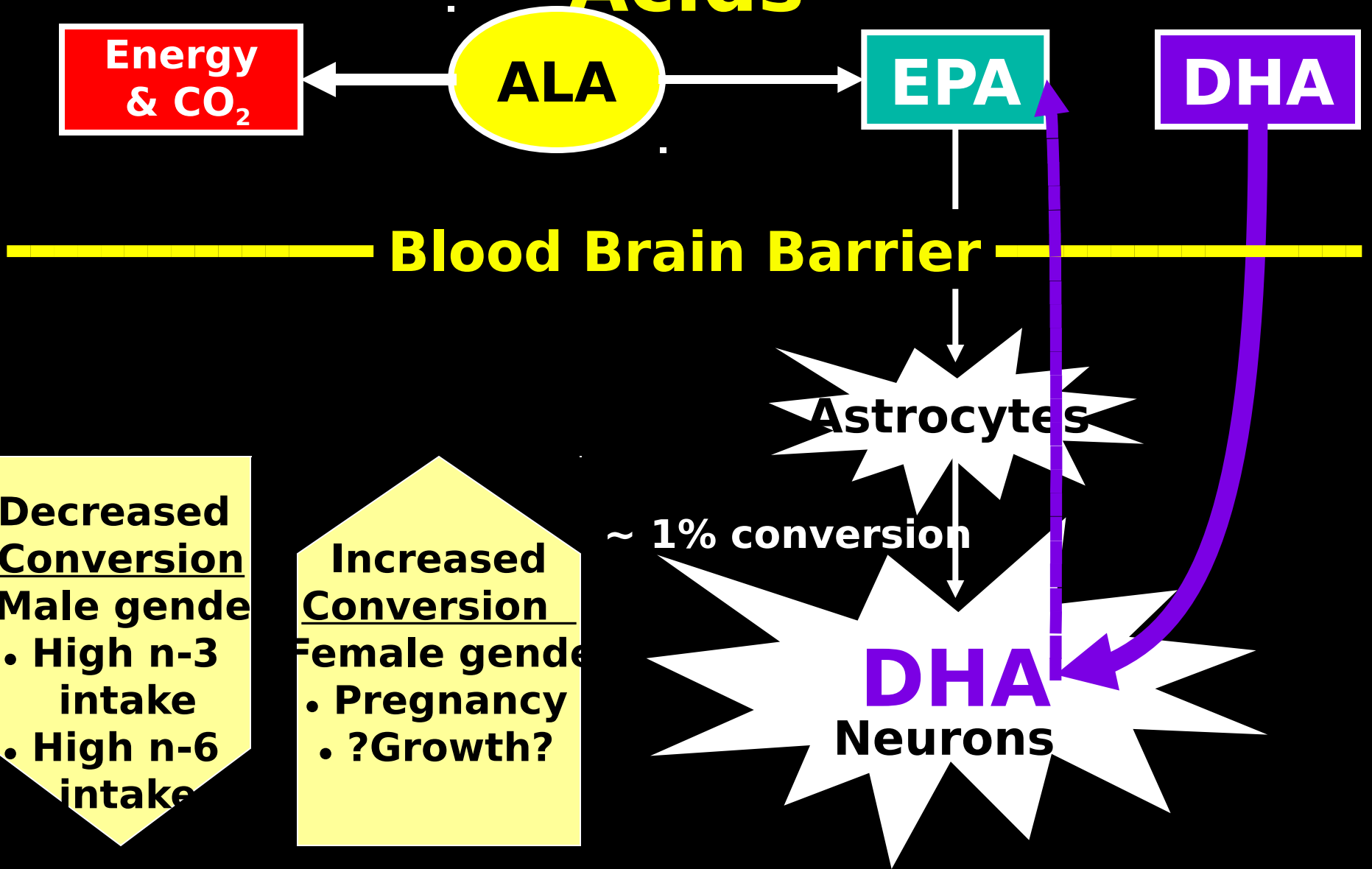

THE DISTINCT HEALTH BENEFITS OF
OMEGA-3s
Cognitive development & function
Visual development & function
Inflammation
Cardiovascular function
Inflammation
Cardiovascular function
Supports EFA status
DHA
EPA
ALA

Docosahexaenoic Acid (DHA)



- Omega-3 fatty acid (*22:6 ω3*)
- Found in all tissues; most abundant in neural, retinal and cardiovascular conducting tissue
  - Brain: 97% of n-3 is DHA
  - Retina: 93% of n-3 is DHA
- Facilitates synaptic transmission
- Supports myelination - influences the speed that information is acquired and processed

Conversion of Omega-3 Fatty Acids



US Dietary Intake is Low

	Recommended Daily DHA Intake*	Average Daily DHA Intake
Pregnant/ Lactating Women	300 mg	54 mg
Adult Women	220 mg	61 mg
Adult Men	220 mg	78 mg

*Expert panel convened by NIH/ISSFAL.

Simopoulos AP, et al. *J Am Coll Nutr*. 1999;18:487-489.
Benisek D, et al. *J Am Coll Nutr.* 1999;18:543-544.
Benisek D, et al. *Obstet Gynecol.* 2000;95:77S-78S.

Some Effects of Lower Brain DHA from Animal Models

- Lower visual acuity
- Changes in attention that suggest slower brain maturation
- Higher impulsivity and reactivity
- Increased stereotyped behavior
- Alterations in brain dopamine and serotonin

DHA is Important *Throughout Life*






Pregnancy

Maternal Health & Outcomes

- Promotes maternal DHA status
- Increases DHA content of breast milk
- Supports normal gestation period
- Promotes fetal brain and eye

Infants & Children

Brain Development & Function

- Improves visual acuity
- Promotes Cognitive performance

Children & Adults

Cardiovascular Heart Health

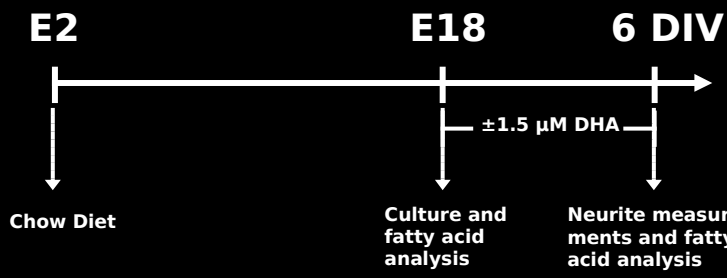
- Lowers triglycerides
- Increases HDL
- Improves blood vessel function

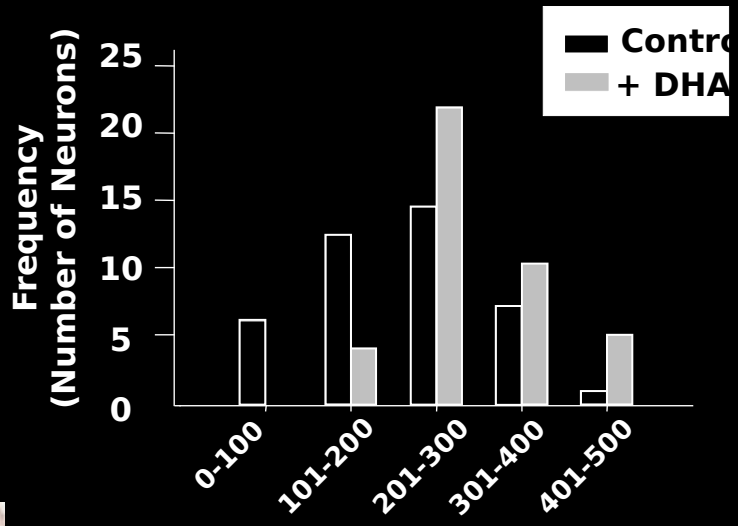
Adults

Brain & Eye Health and Function

- Less cognitive decline
- Lower risk of dementia
- Lower risk of age-related macular degeneration

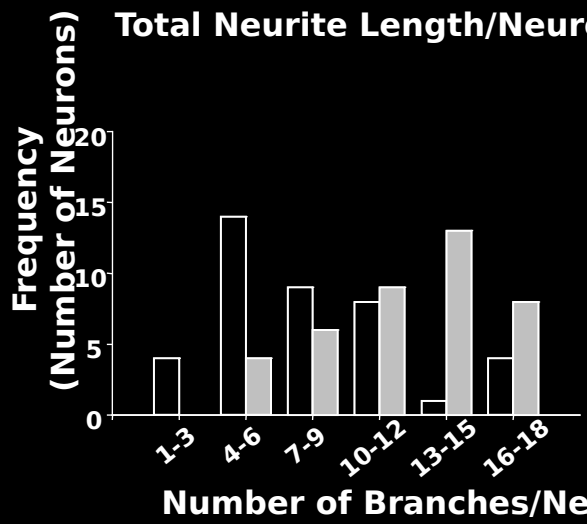
Neurite Outgrowth Enhanced by DHA





Control

+ DHA



Calderon and Kim, J. Neurochem. 200

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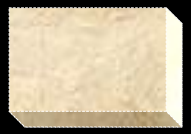
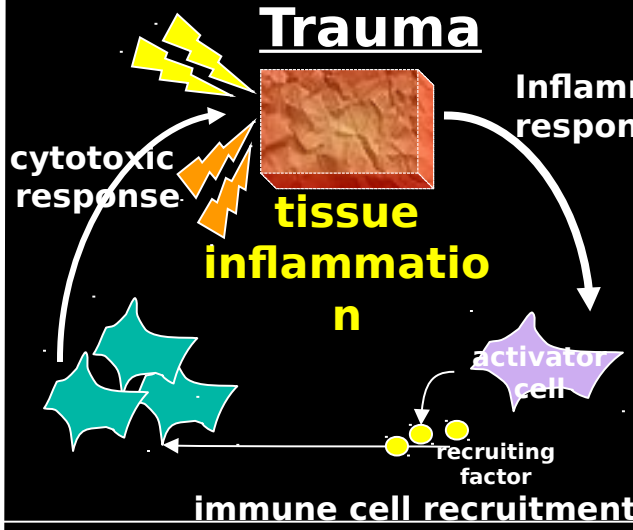
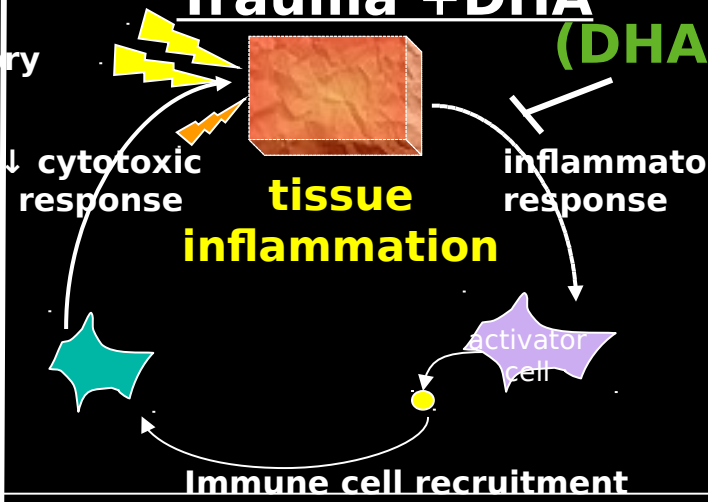
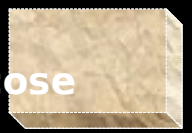
DHA reduces tissue damage caused by trauma-induced acute inflammation

Treatment	Normal	Trauma	Trauma +DHA (DHA
Tissue			
Resolution Process		+ROS stress +reduced ROS defense +membrane degradation +cell death +inflammation +hyperglycolysis	↓ ROS stress ↓ membrane degradation ↓ cell death ↓ inflammation + ROS defense normalized glucose homeostasis
Outcome			
Normal function		Altered neurotransmission (impaired cognitive function)	Normalized function (improved cognitive function

Babcock et al., J Neur Sci;2006;26, 12826-37
Cao, et al., Pharm, Biochem and Behavior;2004;79,651-659
Lee et al., JBiol Chem;2004;279, 16971-79
Weatherill, et al., J Immunology;2005;174, 5390-97.
Wu, et al., J Neurotrauma; 2004;21, 1457-67
Wu, et al., J Neurotrauma; 2007; 24, 1587-95

Efficacy of Clinical Interventions

Meta-analysis of 97 randomized controlled trials:

(Studer M, et al. Arch Intern Med. 2005; 165(7): 725-730)

137,140 in intervention & 138,976 in control groups

Risk Ratios for Overall Mortality

0.77 for n-3 fatty acids
0.84 for resins
0.87 for statins
0.96 for niacin
0.97 for diet
1.00 for fibrates

Risk Ratios for Cardiac Mortality

0.68 for n-3 fatty acids
0.70 for resins

DHA Improves Outcome in SCI

Huang et al. Brain (2007), 130, 3004-3019

- **Experimental SCI in rodents DHA vs. placebo**
- **DHA given 30 min after SCI – locomotive recovery and histologic outcomes substantially improved from day 4, further improvement if fed DHA diet to 6 weeks**
- **DHA ineffective if treatment delayed to 3 hours or if only given by diet x 1 week**

Fish Oil in Critical Illness

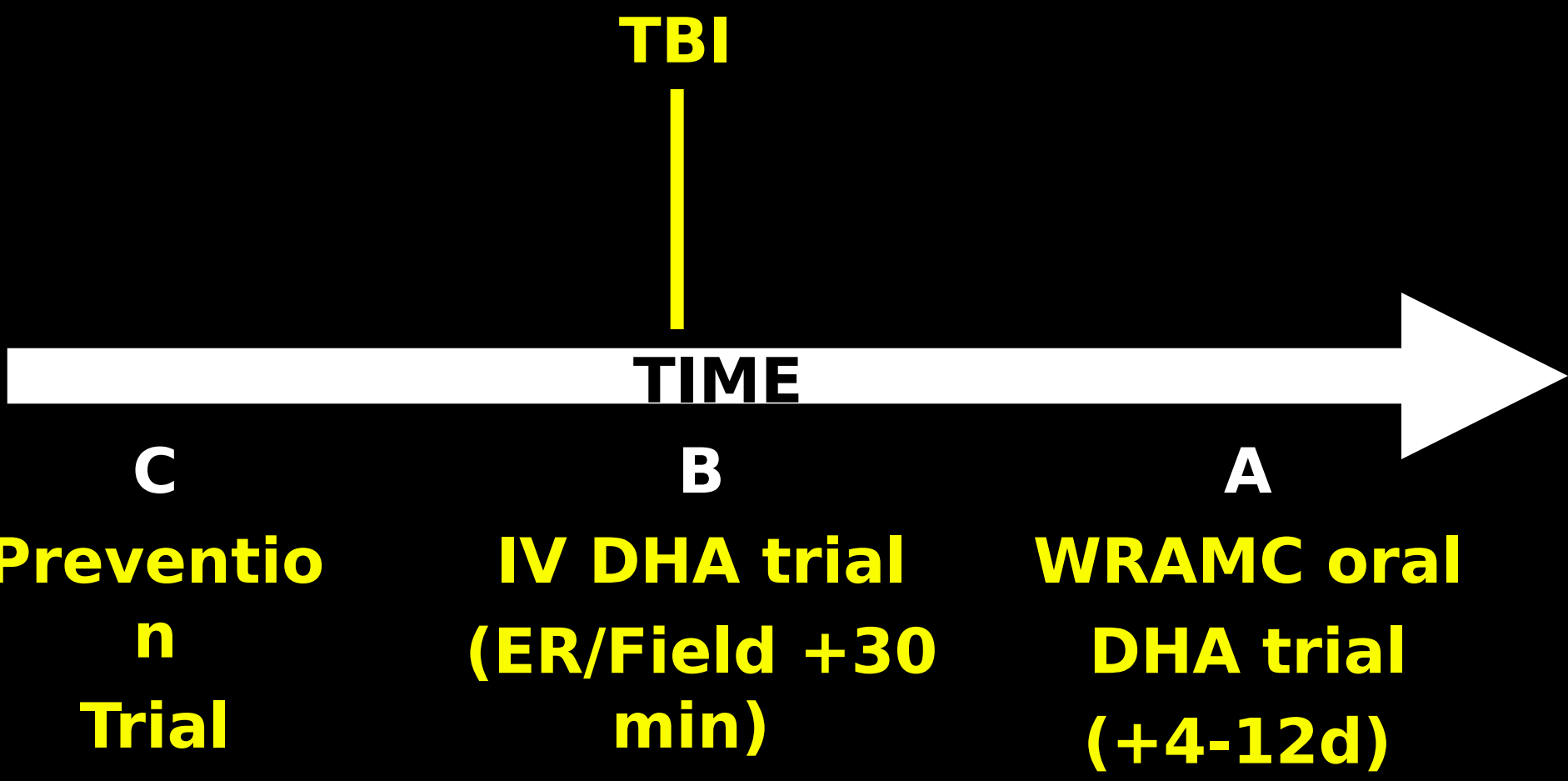
Review Article: Mayer and Seeger. Curr Op in Clin Nutr and Metab Care (2008) 121-127

- **160 cardiac pts randomized to receive 2g FO from -5d pre-surgery to discharge**
  - **Decreased a-fib and LOS**
- **44 major abd surgery pts received n-3 TPN**
  - **No coagulation or platelet abnormalities**
  - **Improved liver and pancreatic function**
- **Several other surgery and trauma studies**
  - **Significant ↓ ventilation, LOS, ICU, mortality**

Upcoming USU/NIH Study: Serologic EFA Status & Suicide

- DoD serum repository
- Compare EFA status of completed suicides since 2002 to age/gender matched controls
- Compare in-theatre and within 2 yrs redeployment to no deployment in 5 yrs
- Adjust for previous psych diagnosis
- Will be the largest such study to date (x100)

Upcoming and Future DoD Studies



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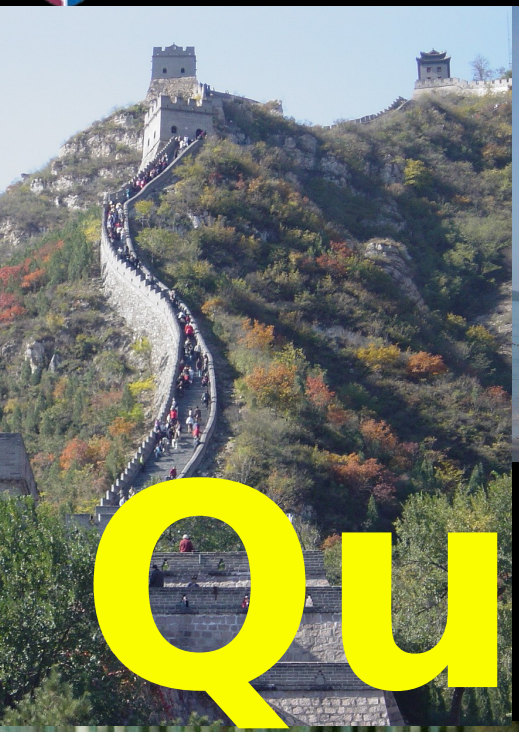
  - **Steve Dubin – CEO**
- **NIH / NIAAA**
  - **CAPT Joe Hibbeln, MD**
  - **CDR John Umhau, MD, MPH**



Questions?